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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,630	04/01/2005	Rajesh S. Gokhale	300622004601	1769

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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
NASHED, NASHAAT T	

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1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,630	GOKHALE ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-40* is/are pending in the application.

4a) Of the above claim(s) *36-38 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election with traverse of Group I, claims 33-35, and the species of SEQ ID NO: 18 in the reply filed on September 25, 2007 is acknowledged. The traversal is on the ground(s) that it is not difficult to examine both Groups in the same application. This is not found persuasive. In order for two inventions to be properly, the invention must meet two requirements. The two inventions must be distinct, and examining the two invention together represents a search burden on the examiner. The inventions are distinct because they require different structural elements. One invention requires an intra-molecular linker, whereas the other requires inter-molecular linker. Thus, a separate search must be carried out for each invention, which represents a search burden on the examiner. With regard to U. S. patent 6,753,173, applicants should note that the restriction between two inventions is at the discretion of the examiner and two examiners may exercise their discretion differently. In this case, this examiner met his burden of establishing the two inventions are distinct and require two different searches in the patent and non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 33-35 and 39 are under consideration.

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/500,747 and 10/091,244, filed February 9, 2000 and March 4, 2002. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless

previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Priority Date for the Pending claims:

Since the claimed invention is neither described nor enabled in provisional application serial numbers 09/500,747 and 10/091,244, or provisional application 60/361,758, the priority for the instant claims is that PCT/US03/06910, filed March 4, 2002.

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the lettering in Figures 31A and 31B is too small to see the details of the Figures. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claims 33 and 34 are objected to because of the following informalities: (a) the phrase "formed from" in claim 33, first line, is repeated twice; (b) On line 10 of claim 33, the phrase "N-terminus of a intra-molecular linker" should be "N-terminus of an intra-molecular linker"; and (c) each sequence identification number should be inserted following the protein name as required by the sequence rules. Appropriate correction is required.

The specification is objected to under 37 CFR 1.57 because the specification improperly incorporate essential subject matter by reference. Section 608.01, under the subheading 37 CFR 1.57 part (c) states:

> (c) "Essential material" may be incorporated by reference, but only by way of incorporation by reference to a U.S. patent or U.S. patent application

publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:

(1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of **35 U.S.C. 112**;

(2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of **35 U.S.C. 112**; or

(3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of **35 U.S.C. 112**.

At page 68, paragraph, first paragraph, the specification referenced NovH to Chen *et al.* (2001) Chem. Biol. 74, 1-12, which is the only description of NovH. Said reference is neither a U. S. patent nor U. S. patent application publication. The subject matter of the improper incorporation by reference is an essential subject because it is being claimed. See claim 35.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The description of NovH is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). See the improper incorporation by reference above.

Claims 33, 34, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 33-35 are directed to a hybrid non-ribosomal peptide synthase (NRPS) and a polyketide synthase (PKS). Said

NRPS part of the hybrid consists of adynylation domain and a peptidyl carrier protein. While there are several NRPS gene clusters are known in the art, the specification failed to define or exemplify the NRPS domain that can be used in the invention. It is noted that the specification identified NovH domain as an example of NRPD domains of the invention, but the specification does have any description or structure for the NovH or any other NRPS domain to be used in the invention. See above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-35 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "an acyl transferase protein (ACP) domain" renders the claim indefinite because the resulting claim does not define the metes and bound of the patent protection desired. For examination purposes only, the phrase is assumed to mean "acyl carrier protein".

(b) Claim 33 recites the limitation "whereby the RAL affect the transfer of a polypeptide chain from said first module to said PKS module". There is insufficient antecedent basis for this limitation in the claim.

(c) The clause "does not natively interact" in claim 33 renders the claim indefinite because the resulting claim does not define the metes and bound of the claimed invention. The phrase is not defined in the specification and one of ordinary skill in the art would not know its meaning. Applicants should note that many NRPS clusters contain several NRPS domains as defined by the claim and one of ordinary skill in the art would not know which ones are within the scope of the claim. Since the gene cluster operates as single synthase and the proteins of the cluster oligomerize to produce the synthase, one of ordinary skill in the art would expect that all domains within a cluster interact with one another. For examination purposes only, the clause taken to mean any NRPS domain.

(d) Claim 35 recites the limitation "wherein said first module comprises PCP domain .....and said second module". There is insufficient antecedent basis for this limitation in the claim.

(e) The term "NovH" renders the claim indefinite because the term is not defined by the specification, and one of ordinary skill in the art would not know what it is. It appears that it refers to an open reading frame or part thereof of novobiocin reported by Chen *et al.* (2001) Chem. Biol. 74, 1-12. Applicants should note that naming genes and their protein product is the purgative of the authors of a scientific article.

(f) Claim 34 and 39 are included in this rejection because it is dependent on claim 33 and do not cure its deficiencies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gokhale *et al.* [Science (April 16, 1999) Vol. 284, 482-485] in view of Pfieifer *et al.* [Science (March 2, 2001) Vol. 291, 1790-1792], Du *et al.* [Abstract, Medline, Accession number 2001301512, Jan. 2001], and Marahiel *et al.* [Chem Rev. (1997) 97, 2651-2673].

Gokhale *et al.* teach that short intermodular linkers play a crucial role in the assembly of functional modules as well as in the intermodular polyketide chain transfer. See page 483, left column, second half. Figure 3 at page 484 show the amino acid sequences of the linker including that of M2 ery of SEQ ID NO: 18. Gokhale *et al.* teach that, with appropriate selection of linker, it is possible to facilitate communication between heterologous modules. They replaced M2 module of DEBS with M5 of rifumicin polyketide synthase from *Amyeolyatopsis mediterrunei* and show that the recovered the same product with similar efficiency. See page 485, left column. In

addition they teach that greater degree of freedom diversity in polyketide structures could be combinatorially accessed through the interweaving of PKS modules with those of non-ribosomal peptide (NRPS) synthase. See the paragraph bridging pages 482 and 483. Gokhale *et al.* does not teach a hybrid formed from NRPS module and PKS module, wherein the NRPS module contains an adenylation domain (A) through the peptidyl carrier protein (PCP) and the A domain does natively natively interact with a PKS domain.

Pfiefer *et al.* teach a hybrid NRPS-PKS consisting of the loading module of NRPS comprising the A and thiolation domain [also known as peptidyl carrier protein domain (PCP domain)] in which said loading module replace the DEBS loading module which produces novel polyketides. See Figure 1. Phieifer *et al.* do not teach NRPS-PKS hybrid wherein the NRPS module does not natively interact with a PKS domain.

Du *et al.* teach that: (1) the same catalytic sites are conserved between the hybrid NRPS-PKS and normal NRPS or PKS systems, although the KS domain in NRPS/PKS hybrid is unique; and (2) the linker between the C-terminal of of the NRPS protein and N-terminal of the PKS protein play critical role in facilitating the transfer for the growing peptide or polyketide. See the entire abstract.

Marahhiel *et al.* is a general review article about the modular structure and function of NRP. Applicants attention is directed to page 2659, right column second paragraph. It teaches that the adenylation domains are structurally and functionally independent and they are highly homologues. They can be swapped so many peptide product can be produced.

Both Gokhale *et al.* and Pfiefer *et al.* provide one of ordinary skill in the art with motivation to make hybrid NRPS-PKS to obtain divers analogs of polyketides and cyclic peptides which are known to have important biological activities. Gokhale *et al.*, Pfiefer *et al.* and Du *et al.* provide the ordinary skill in the art with motivation to insert the intramolecular linker between the NRPS module and the PKS module as they teach the important of the linker for proper channeling the product of one module to the other. Thus, it would have been obvious at the time of invention to one of ordinary skill in the art to construct an expression system as that taught by Gokhale *et al.* or Pfieifer *et al.* comprising a nucleic acid sequence encoding NRPS's module comprising at least A domain and PCP including one of the known NovH domain linked to the coding sequence of a linker peptide such as that of SEQ ID NO: 18 taught by Gokhale *et al.* followed by the coding sequence of PKS domain such as module 1 and 2 of the DEBS gene cluster along with the rest of DEPS gene cluster as taught by Pfiefer *et al.* to produce analogs of 6-dEB (claim 33-35) by culturing the host cell comprising (claim 39).

It is noted that the claims specify that the NRPS module is naturally associated with a PKS domain and the specification states:

> "Although an artificial intrapolypeptide NRPS-PKS interface has previously been created by replacing the DEBS loading didomain with the rifamycin synthetase A-PCP loading didomain (Pfeifer, et al., (2001) Science 291, 1790-1792), the rifamycin A-PCP didomain naturally interacts with PKS domains on the same polypeptide, indicating that it may be inherently more amenable to engineering into alternate NRPS-PKS junctions. In contrast, this experiment with NovH(4) is to our knowledge the first example of engineering a functional NRPS-PKS interface involving an NRPS domain that does not naturally interact with any PKS proteins and a PKS domain that does not naturally interact with any NRPS proteins. While this experiment biases the transfer reaction by eliminating the small molecule recognition component of a true NRPS-PKS transfer, it indicates that the heterologous linker regions are sufficient for inducing interaction between two naturally non-interacting proteins and illustrates the potential of these linker regions for future engineering of artificial interpolypeptide junctions." See specification, paragraph 136 at page 36.

Despite the above, one of ordinary skill in the art would have had a reasonable expectation of obtaining a functional hybrid NRPS-PKS from the teaching of the prior art. First, the only domain in the NRPS module to interact with the KS domain is PCP domain. Although Du *et al.* teach that the KS domain of the natural NRPS-PKS hybrid is unique, Pifiefer *et al.* teaching shows that PCP of the NRPS module interacts efficiently with KS domain of PKS. Since all KS domains are interchangeable and all domains are functionally independent in both NRPS and PKS, one of ordinary skill in the art would have expected success in obtaining the functional heterologus NRPS-PKS hybrid. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nashed/
Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656